Aging and Disease
www.aginganddisease.org
Volume 2, Number 2; 181-185, April 2011

Perspectives

Aging and Transplantation – A Topic for Biomedicine or Bioethics?

William J. Hubbard[1*] and Nassrin Dashti[2]

University of Alabama at Birmingham, [1]Department of Surgery, Center for Surgical Research and [2]Department of Medicine, Division of Gerontology, Geriatrics and Palliative Care

[Received February 10, 2011; Revised February 18, 2011; Accepted February 21, 2011]

ABSTRACT: The aged patient stands at the nexus of significant biomedical and bioethical issues in transplantation. This in itself can be seen as a microcosm of an imminent global tempest, stemming from expanding numbers and longer lives of the aged population. As a candidate for receiving organ and tissue transplants, the geriatric patient is challenging because they present unique physiology for medical management. As organ and tissue donors, the aged are perceived of as providing "marginal" organs, which drives the fear that the graft will fail before the recipient. Such difficulties lead inexorably to several unique bioethical considerations for transplantation with this population. The thorny conundrums for society hinge on fairness versus discrimination based on age, played out under the enormous and probably intractable problem of severe donor organ shortages. Fortunately, recent findings offer some rather unexpected new and favorable prospects. Notably, aged donors can provide organs with good, lifesaving function, even though there are nonetheless age-related compromises present. On the other side of the coin, there is less doubt that recipients can have their lives extended with high quality through transplantation. Here they benefit from some (counterintuitively) positive attributes for aging, such as reduced immune function, making immunosuppression less rigorous. Finally, the pressure of organ and tissue shortages plus the lifting of bans on embryonic stem cell research have portents for an explosive alternative to transplantation of adult organs. Stem cells also lend credibility to prospects for realizing regenerative medicine, assuming ethical and religious concerns can be satisfied.

Key words: Transplant; Aging; Donor; Recipient; Immunosuppression; Immunosenescence; Bioethics; Embryonic Stem Cell; Adult Stem Cell

When confronting the subject of transplantation in aged populations, one is struck by the timeliness of the topic. For example, in the United States, the much anticipated and essentially simultaneous retirement of the so called "baby boomers" has demanded an urgent shift in attention toward an aging population. Of all the medical options for treating diseases of aging, transplantation reveals the inextricably-linked duality of medical and societal concerns for care of the older person. Thus this mini-review will touch on both areas, namely the biological and medical aspects of transplantation, as well as the societal and bioethical concerns superimposed on the process of selecting and matching donors and recipients.

Biomedicine of Older Recipients

As with all stages of life, for aging there are medical up- and down-sides. At first blush, it would seem that the balance sheet for a geriatric organ or cell transplant recipient is rather steeply biased toward the negative. The patient is often frail and compromised, with attendant reduced function in organ systems. This obviously arises both from age *per se* and the cumulative effects from the underlying disease(s) which led to organ failure. Other obvious factors such as infectious disease and substance abuse can add to the detriment of the graft, but there is an increasingly acute awareness that atherosclerosis, hypertension, hyperlipidemia and

***Correspondence should be addressed to:** William J. Hubbard, University of Alabama at Birmingham, 1670 University Drive, Volker Hall G-094, Birmingham, AL 35294, USA. **Email:** bhubbard@uab.edu

ISSN: 2152-5250

diabetes are major risk factors that must be mitigated [1,2]. As such, the causal pathologies for organ failure can continue to work their deleterious effects at some indeterminate rate on the graft. Thus there are multiple vulnerabilities for the older transplant recipient, superimposed upon the conspicuous issue of shorter life expectancy and the higher burden of comorbid conditions [3]. Kidney transplantation provides abundant examples of hurdles for the older recipient, given that it is the most prevalent and mature type of transplantation. For example, the damage from rejection episodes to the kidney graft is exaggerated in the older recipient, and nonspecific nephrotoxicities from immunosuppressive drugs are more pronounced and unpredictable [1,4]. It can fairly be said that such delicate, complex and intensive management problems present a disincentive for the clinician to treat geriatric transplant recipients.

Fortunately, there are upsides to aging for the transplant recipient as well. The decline of the potency of the immune system with aging, the so-called phenomenon of immunosenescence, exists where the helper T cell (i.e., $CD4^+$) population is less functional *in toto.* This has implications that older persons are more susceptible to infections and neoplasms, which are otherwise under constant surveillance by the immune system. However, this status has the offsetting benefit of making the management of immunosuppression in the older individual a less rigorous and aggressive proposition. One fascinating insight into this phenomenon can be found with regulatory T cells (T_{reg}), which are also referred to by their phenotype of $CD4^+CD25^+$. The T_{reg} is the long sought-after suppressor T cell. It functions in a homeostatic fashion to dampen and down-regulate an immune response after the threat is cleared. This winding-down can be mediated by secretion of the "suppressor" cytokine IL-10. With aging, these cells accumulate in number and diversity, rendering the individual less responsive immunologically to an allograft [5]. These assertions of immune-senescence and T_{reg} suppression are generally supported by a recent retrospective study which concluded that matching the ages of donor and recipient had the effect of easing the manifold transplant stresses on both donated kidneys and older recipients [6]. To quote the authors:

> "*Our results show that increasing recipient age is associated with an improved transplant survival, lower rates of rejection, and superior outcome of older donor organs. Physiological and/or immunologic aspects of organ and recipient age seem to determine, at least in part, the success of renal transplantation.*"

The somewhat surprising aspect of this study was that the aged kidney seems to fare better in an aged donor, even though they were less well matched and of poorer quality. One wonders whether an age-related dampening of the "passenger lymphocyte syndrome" (which leads to a harmful graft-versus-host response [7]) associated with solid organ transplantation might enter into the equation, since these cells were likely to be immunosenescent as well.

Scientific and medical issues and arguments notwithstanding, the proof for recipient suitability for the aged is still "in the pudding", so to speak. In an extensive retrospective study of kidney allograft recipients, the 5 year survival statistics for recipients and grafts were analyzed for age groups 50-60, 60-65, and older than 65. There was a modest enhancement in patient survival for the 50-60 year old group, with no great survival difference of the graft for all age groups [8]. The authors concluded that "Discrimination against older candidates for kidney transplantation on age-related grounds alone is not warranted".

The Stem Cell Fix

While organ transplantation is problematic simply because it involves a finite and indeed shrinking supply of terminally differentiated tissues, stem cell transplantation offers the prospect of a potentially limitless supply of transplantable cells, owing to their ability to proliferate *in vitro*. These cells in turn have the potential to repair and replace damaged or lost tissues. Furthermore, the immunosuppressive management issues are likely to be diminished due to "immune privilege" for stem cells. This widely-held belief is, however, being tempered by findings of unique allogeneic responses directed toward these progenitor cells [9]. Fortunately, the stem cells themselves can exert immunosuppression, which can be manipulated to advantage [9]. While the United States' highly restrictive policy of the prior decade for the use of embryonic stem cells in research has been a setback, the recent lifting of these constraints holds promise for an explosion of innovation. Indeed, roughly 60% of stem cell research involves transplantation, of which three-fourths are allogeneic [10]. What is so very intriguing about stem cell transplantation is that this methodology can not only correct organ/system failures, but it also holds the prospect of reversing some aspects of aging *per se*, coming under the rubric of "regenerative medicine" [11].

Regenerative medicine is obviously not limited solely to the use of embryonic stem cells. Strategies based on adult stem cells have been enticing simply because they avoid the obvious bioethical and religious pitfalls of

being derived from embryos. Adult stem cells are also present in many tissues, which concomitantly establishes an organ- or tissue-specific commitment, avoiding the vagaries of pleuripotency; i.e., there is little concern that they may develop in an unanticipated or problematic direction. If adult stem cells are isolated and expanded, many possibilities for regeneration are opened. For example, in the heart, cardiac stem cells (CSC) are distributed throughout the organ, and remain active from embryogenesis through adulthood. Transplantation of CSC holds promise for restoring damaged tissues and ventricular function [12]. Furthermore, in the near future it may be possible to circumvent transplantation altogether, since it is possible to activate the resident CSC via the local delivery of growth factors, or through systemic injection of cytokines and/or drugs such as statins, which have many pleiotropic effects [12]. Of particular interest is the prospect for reversing or ameliorating cognitive disorders. While improvement in lifestyle such as exercise, caloric restriction and enrichment of the environment can have positive effects for the slowing of neurological maladies such as Alzheimer's disease, it may also be possible to marshal endogenous neurological stem cells (or stem cell transplants to the brain) to lessen the disease and its progression [13].

Biomedicine of Aged Donors

The widespread scarcity of donor organs is forcing a reevaluation of criteria for donor suitability, and a new willingness for the use of geriatric cadaveric donors. This fact is verified by an increasing median age of kidney donors [1]. However, as one would expect, the aged graft is less robust as compared to one from a younger donor, and the ability to recover from damage decreases with age [4]. For example, it is anticipated that with kidney grafts from donors older than 50 years, there is less renal mass with fewer functioning nephrons [4]. Still, the unstated but obvious fact is that, unlike the unpredictable wait for a younger person's chance death to provide cadaveric donor organs, the aged are nearer the end of natural life and would seem *a priori* to offer a more reliable donor supply. The challenge for the transplant community would be to manage these so-called "marginal" organs, with reduced function and viability [1]. Accordingly, efforts are being made to understand the nature of deficiencies for aged organs and to optimize the function of the graft. A good example of this effort can be found with liver transplants donated from cardiac death patients, which are more likely to be aged individuals. It has been recognized that liver grafts from cardiac death donors can have both their survival and function enhanced by shortening ischemic times and improving surgical procedures, along with more "front end" attention being placed on perioperative techniques and donor selection criteria [14].

Analyses of results from liver transplantation have also produced an additional interesting observation, namely that the age of the organ donor may be less important than the particular organ itself. As compared to kidneys, hearts and lungs, livers are fairly refractory to the effects of aging, as revealed by a retrospective study of liver donors [15]. This study had the remarkable finding that healthy 80 year old donors can provide well-functioning livers. It should be noted that the livers were not without defects associated with aging, e.g., they typically exhibited reduced size, lessened Kupffer cell phagocytotic activity, lower protein synthesis, reduced endothelial cell endocytosis, lowered blood flow, etc. These deficiencies were offset by the large functional reserve of the organ, coupled with its regenerative capacity and dual blood supply. Interestingly, the authors also reported that the liver was less affected by atherosclerosis for unknown reasons [15]. We would speculate that this phenomenon may be a result of the liver's high capacity to convert cholesterol to bile salts, an active process that quantitatively represents the major route of cholesterol excretion (removal) from the body [16]. As a fascinating aside, it is possible that, through the action of the bile salt receptor FXR and the bile acid receptor TGR5, even depot cholesterol distal to the liver in atherosclerotic lesions can be "unloaded" [16]. Thus the placement of a functioning liver may have unanticipated side benefits.

Finally, the clear concern for the use of aged donor organs is found in the implicit prospect of reduced viability of the donated organ, such that the recipient will outlive the organ graft. This centers on the losses of several functions of the organ with progressive nature of aging, the consequence of which is lessened abilities to correct and repair defects. This topic is covered succinctly in a review by Naesens [17], dealing with cellular replicative senescence in normal processes and transplantation, a topic which is obviously applicable to both the graft and aged recipient. By examining the transcriptsome, it has been determined that aging is reflected in small changes in transcription of many genes, rather than large changes in a few genes. This is revealed phenotypically as the loss of the ability to grow, or "replicative senescence", which is irreversible. While the loss of telomeric function with attendant failure of mitotic competence is the cytological hallmark of cellular senescence, the underlying molecular events are becoming better understood. Nasens [17], has collated the current literature to construct an integrated picture

where two pathways, p53 (i.e., the cell cycle and tumor suppressor protein) and p16 (likewise a cell cycle regulator and tumor suppressor, plus stabilizer of p53), converge to promote senescence. The upstream signals arise from telomeric shortening, DNA damage (e.g., oxidative damage, irradiation, etc.), chromatin perturbation and repeated mitotic signals from oncogenes, with the ultimate outcome of senescence or growth arrest [17]. Thus the invocation of the p53 pathway obviously links the process with the positive benefit of tumor suppression, but in so doing, the negative consequence is seen in the incremental loss of function for tissue repair.

Bioethics and Aging

The dilemma to equitably balance fairness versus pragmatism in access to medical care is arguably most illustrative in transplantation. Science fiction is now the stuff of reality, and organ shortages and extremely high costs of transplantation and its management have necessitated the consideration of rationing for donors and recipients. It is a sobering and disappointing fact that, while transplant science has improved the success rate dramatically over time, the numbers of donors, both living and cadaveric, has declined steadily [18]. This portends the pitting of our burgeoning aging population against the younger populace, who have their productive years ahead of them. These harsh determinants are presently playing out in the context of health care reform in the United States. Accordingly, this issue had driven out a proposed protocol/algorithm to assess kidney transplant recipient eligibility, namely the "Life Years from Transplantation" (LYFT) system, created under the auspices of the preeminent United Network for Organ Sharing [19]. What is fascinating about the LYFT proposal was that it failed to be adopted, not unexpectedly because of negative ethical considerations (i.e., rationing that disfavored the aged), but more interestingly because of the system's overall poor accuracy in predicting optimum benefit from transplantation.

However, the demise of LYFT hardly makes the thorny issues of aging go away. It was noted that the impetuses for such a system were an increased waiting time for potential recipients, increased morbidity and mortality for wait-listed patients, and poor kidney graft survival in aged recipients [19]. Because the average age of kidney transplant recipients is steadily increasing, the passage of time will only exacerbate these problems, owing to the two-edged sword of greater life expectancy resulting from improved medical understanding and practice. One can clearly see an analogy between transplantation and "peak oil", where, just as we have long passed the point of being able to extract the relatively economical, abundant and accessible oil deposits, we have likewise long passed the point of easy availability for organ donation. Indeed, allogeneic organ and tissue (e.g., bone marrow and pancreatic islets) may realistically be considered the harvested "low hanging fruit". Thus, new options are needed to augment therapeutic transplant strategies, and they need to emerge with deliberate haste.

Perhaps it is time to consider promoting greater incentives to the transplant research community in order to realize alternative to the current technology of allotransplantation. Strategies already in development such as xenotransplantation or design of artificial organs could and should be expanded in effort and scope. For example, a promising alternative to the difficult aim of xenotransplantation of adult organs is found with the use of embryonic pig organs, primordia or pancreatic islets in experimental animal testing [20]. While the concept is proven, it does require immunosuppression for the recipients (rats and macaque monkeys). In a similar vein, it would be extremely advantageous to boost the priority for realizing a robust means to induce transplant tolerance, which could greatly decrease the stringency of donor-recipient matching as well as extending the functional life of donated organs. By accelerating the arrival of these technologies to a make or break decision point for clinical translation, large returns could potentially be reaped. Necessity is indeed the mother of invention.

REFERENCES

[1] Stallone G, Infante B, Gesualdo L (2010). Older donors and older recipients in kidney transplantation. J Nephrol, 23 Suppl 15**:** S98-103.

[2] Slynkova K, Mannino DM, Martin GS, Morehead RS, Doherty DE (2006). The role of body mass index and diabetes in the development of acute organ failure and subsequent mortality in an observational cohort. Crit Care, 10(5)**:** R137.

[3] Aucella F (2010). Epidemiologic and clinical challenges of geriatric nephrology. J Nephrol, 23 Suppl 15**:** S1-S4.

[4] de Fijter JW (2005). The impact of age on rejection in kidney transplantation. Drugs Aging, 22(5)**:** 433-449.

[5] Wang L, Xie Y, Zhu LJ, Chang TT, Mao YQ, Li J (2010). An association between immunosenescence and CD4(+)CD25(+) regulatory T cells: a systematic review. Biomed Environ Sci, 23(4)**:** 327-332.

[6] Tullius SG, Tran H, Guleria I, Malek SK, Tilney NL, Milford E (2010). The combination of donor and recipient age is critical in determining host

immunoresponsiveness and renal transplant outcome. Ann Surg, 252(4)**:** 662-674.

[7] Audet M, Panaro F, Piardi T, Huang P, Cag M, Cinqualbre J, Wolf P (2008). Passenger lymphocyte syndrome and liver transplantation. Clin Dev Immunol, 2008**:** 715769.

[8] Fabrizii V, Winkelmayer WC, Klauser R, Kletzmayr J, Saemann MD, Steininger R, Kramar R, Horl WH, Kovarik J (2004). Patient and graft survival in older kidney transplant recipients: does age matter? J Am Soc Nephrol, 15(4)**:** 1052-1060.

[9] English K, Wood KJ (2010). Immunogenicity of embryonic stem cell-derived progenitors after transplantation. Curr Opin Organ Transplant.

[10] Eve DJ, Fillmore RW, Borlongan CV, Sanberg PR (2010). Stem cell research in cell transplantation: sources, geopolitical influence, and transplantation. Cell Transplant, 19(11)**:** 1493-1509.

[11] Mironov V, Visconti RP, Markwald RR (2004). What is regenerative medicine? Emergence of applied stem cell and developmental biology. Expert Opin Biol Ther, 4(6)**:** 773-781.

[12] Torella D, Indolfi C, Goldspink DF, Ellison GM (2008). Cardiac stem cell-based myocardial regeneration: towards a translational approach. Cardiovasc Hematol Agents Med Chem, 6(1)**:** 53-59.

[13] Lazarov O, Mattson MP, Peterson DA, Pimplikar SW, van PH (2010). When neurogenesis encounters aging and disease. Trends Neurosci, 33(12)**:** 569-579.

[14] Reich DJ, Hong JC (2010). Current status of donation after cardiac death liver transplantation. Curr Opin Organ Transplant, 15(3)**:** 316-321.

[15] Singhal A, Sezginsoy B, Ghuloom AE, Hutchinson IV, Cho YW, Jabbour N (2010). Orthotopic liver transplant using allografts from geriatric population in the United States: is there any age limit? Exp Clin Transplant, 8(3)**:** 196-201.

[16] Hageman J, Herrema H, Groen AK, Kuipers F (2010). A role of the bile salt receptor FXR in atherosclerosis. Arterioscler Thromb Vasc Biol, 30(8)**:** 1519-1528.

[17] Naesens M (2011). Replicative senescence in kidney aging, renal disease, and renal transplantation. Discov Med, 11(56)**:** 65-75.

[18] Klein AS, Messersmith EE, Ratner LE, Kochik R, Baliga PK, Ojo AO (2010). Organ donation and utilization in the United States, 1999-2008. Am J Transplant, 10(4 Pt 2)**:** 973-986.

[19] Reese PP, Caplan AL, Bloom RD, Abt PL, Karlawish JH (2010). How should we use age to ration health care? Lessons from the case of kidney transplantation. J Am Geriatr Soc, 58(10)**:** 1980-1986.

[20] Hammerman MR (2011). Xenotransplantation of embryonic pig kidney or pancreas to replace the function of mature organs. J Transplant, 2011**:** 501749.